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Vive la Difference!

The subfields of the primate visual cortex differ in their cytological composition, including the relative width of the layers. In this issue of *Neuron*, Lukaszewicz et al. report that the origin of these laminar, and thus areal, differences can be traced to the kinetics of progenitor cell divisions in the subjacent proliferative zones that generate neurons that migrate radially to the appropriate layers at each side of the cytoarchitectonic border.

The mammalian neocortex is organized into six horizontal cellular layers, designated—from outer to inner—as layers I to VI and is regionally subdivided into particular areas. We are all seduced by the remarkable similarities in cortical organization within and between species, such that we forget that the differences are where we should look for the evolutionary progress that has led to the ascent of our cognitive abilities. For example, the visual cortex in primates can be divided into several subfields with distinct cellular and functional properties not found in other mammals. The cortex of the primary visual area (17 of Brodmann) has more cells per radial unit, including a several-fold thicker layer IV than the adjacent area 18. Furthermore, the borderline between the two areas is obvious and abrupt. This distinction is particularly prominent in human and Old World primates such as macaque monkeys and is considered an evolutionary adaptation essential for more sophisticated visual processing. How such exuberant cytoarchitectonic distinction originates is of interest, not only for understanding normal and pathological development of the visual system in humans, but also because it can give us a hint about how novel cytoarchitectonic features might have emerged during the course of evolution. In this issue of *Neuron*, a group of French neuroscientists show that the difference between these areas involves a regional increase in the number of cell divisions in the embryonic proliferative zones in the occipital lobe that supply the neurons of the overlying cortex (Lukaszewicz et al., 2005). Their study indicates that an essential step in the evolution of cortical elaboration may be an increase in the production of particular types of neurons in selective regions of the proliferative zones.

Although it is well established that the number as well as relative and absolute size of cytoarchitectonic areas can change during evolution, how such a complex cellular rearrangement is achieved remains elusive. Does the cortical surface and its thickness increase uniformly as a sheet of equipotent cells that later become sculpted by the subcortical afferent input, or is there some distinction between prospective areas already present at the time of the cell's exit from the mitotic division within the proliferative zones, as suggested by the protomap hypothesis (Rakic, 1988)? The intrinsic initiation of the cortical map has been supported by reports that a number of genes and morphoregulatory molecules are expressed regionally prior to, or independently of, the incoming input (e.g., Grove and Fukuchi-Shimogori, 2003; O'Leary and Nakagawa, 2002). However, it is also known that input from subcortical structures is essential for the subsequent maturation and regulation of the final size of the cytoarchitectonic areas (e.g., Rakic et al., 1991; Rubenstein et al., 1999). Thus, the present study addresses a conceptually important question: whether the difference in the laminar width, such as observed between areas 17 and 18 in primates, is a result of an increased production of cells destined for area 17 in the subjacent proliferative zones or is due to an increase in the cell death of postmigratory cells in area 18?

Lukaszewicz et al. have performed complex in vivo and in vitro experiments to expose the difference in the kinetics of progenitor cell division in the proliferative zones subjacent to areas 17 and 18. This difference could be predicted from previous studies showing that area 17 develops some of its specific cytological properties even if deprived of the thalamic input (Rakic, 1988; Rakic et al., 1991). Furthermore, it has been shown that cell cycle duration in the ventricular zone (VZ) subjacent to areas 17 and 18 is different at the time when the supragranular layers (i.e., layers II and III) are being generated (Kornack and Rakic, 1998). However, the present study expands these findings by showing that the areal difference in cell cycle duration is associated with changes in levels of expression of the cell cycle regulators $p27^{Kip1}$ and cyclin E. Cyclin E and $p27^{Kip1}$ display reciprocal levels of expression in the two areas, and their ex vivo up- and downregulation modifies the rate of cell cycle re-entry and neuronal production. Progression from the first gap phase of the cell cycle (G1) to the DNA synthesis phase (S) depends on the successful release of the cyclin E-Cdk2 complex from the inhibitory grip of the cdk inhibitor $p27^{Kip1}$. These findings support the evidence from fruit flies and rodents that the G1/S restriction point is a target for genetic manipulation—by p27, Sonic hedgehog, Notch, and particular proneural genes—which in part underlie the evolutionary adaptations of cortical thickness (Ohnuma and Harris, 2003; Tarui et al., 2005). Thus, the G1/S transition may, at least in part, be among the genetic targets underlying these evolutionary adaptations of cortical thickness. Importantly, the supernumerary cells, even in the convoluted primate cerebrum, are not dispersed randomly, but rather follow radial glial guides (Rakic, 1988). This is simple, but conceptually important additional evidence that the first step to the creation of a more elaborate cortex is to produce a larger number of neurons of a given type.

The present study also shows that the embryonic cerebral wall in macaque, similar to human, has a highly expanded subventricular zone (SVZ) with a large outer layer that is not observed in rodents (Figure 1). Again, there may be evolutionary significance in this enormous enlargement. Unlike in rodents, in which most of the interneurons are supplied by tangential migration from

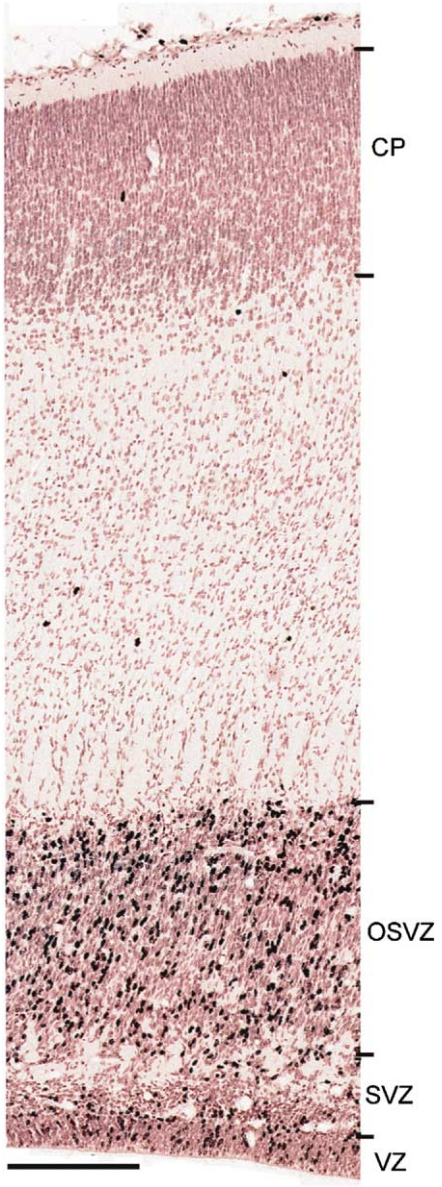

Figure 1. Cerebral Wall of the Monkey Embryo

The section from the cerebrum at 78 postconceptual days in this species illustrates the proliferative ventricular zone (VZ) as well as the uncommonly large subventricular zone (SVZ) with outer layer (OSVZ) both filled with dividing cells labeled with the DNA marker tritiated thymidine (dark profiles). The enlargements of these secondary proliferative zones can be considered as an evolutionary adaptation for a supply of neurons destined for the superficial layers of the overlaying cortical plate (CP). This figure is reproduced from Lukaszewicz et al. (2005), this issue of *Neuron*.

the ventral telencephalon (e.g., Rubenstein et al., 1999), in human, more than half of the interneurons originate in the subjacent SVZ and migrate radially (Letinic et al., 2002). When dividing progenitors in the VZ/SVZ are selectively deleted by exposure of the monkey embryo to ionizing radiation at specific postconceptual days, their progeny are absent in the layers of their destination, with a sharp shift in the depth of the depleted layers at the 17/18 border (Algan and Rakic, 1997). Together, the studies in the macaque monkey visual cortex demonstrate that regional differences in cell production are already detectable in the proliferative VZ and SVZ, before the onset of neuronal migration and differentiation.

The molecular mechanism of areal specification is, however, far from being solved. For example, the present study only opens the door to further analysis of the complex biology of $p27^{Kip1}$, the regulatory effect of its degradation, and its function in cell cycle regulation and related cellular events. This is especially indicated because of recent reports linking $p27^{Kip1}$ to cytoskeletal reorganization by Rho GTPases, which coordinate both migration and cell-cell attachment (Besson et al., 2004). Through the cytoplasmic form of $p27^{Kip1}$, neuronal migration from the VZ and the expansion of the SVZ may depend on the differential activation and deactivation of molecules such as RhoA and Rac. Thus, further studies are needed to elucidate the effect of genetic loss-of-function/gain-of-function manipulations of parallel mechanisms not addressed in this study.

An ancillary benefit of this study is that it shows the value of research on different species. Although the basic principles of cortical development may be the same in all mammals, even small differences in timing of the cell cycle, mode of cell division, or pattern of neuronal migration could have both clinical and evolutionary implications. Since development of the human brain cannot be readily analyzed by experimental methods, it is essential to have this type of data from nonhuman primates, which are relevant to understanding development of the cortex in our own species. As a next step, it is important to isolate region-specific neuronal stem cells and investigate the potential of these progenitors in vitro and in vivo. The subject is timely because the issue of the heterogeneity of neuronal stem cells and their spatial restrictions has recently come into focus among developmental neurobiologists interested in cell replacement therapy. With completion of the gene sequencing of the macaque monkey later this year, such clinically and conceptually important issues could be addressed more directly at the molecular level in the primate cerebral cortex.

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